

# Management of persistent methicillin-resistant *Staphylococcus aureus* bacteremia with 32 days of positive blood cultures

Ramanathan MR<sup>1,2</sup>, Davis S<sup>1,2</sup>, Coker C<sup>2</sup>, Desai D<sup>2,3</sup>

Ramanathan MR, Davis S, Coker C, et al.. Management of persistent methicillin-resistant *Staphylococcus aureus* bacteremia with 32 days of positive blood cultures. *J Basic Clin Pharma* October - 2018;9(3):319-321.

Antibiotic combinations with daptomycin are recommended for persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. This report illustrates a case of successful treatment of a 63-year-old male with persistent MRSA bacteremia with high vancomycin and daptomycin MICs secondary to vertebral osteomyelitis using salvage therapy. The patient was empirically started on vancomycin and piperacillin/tazobactam for the vertebral osteomyelitis; however, due to worsening leukocytosis and lack

of clinical improvement with vancomycin, the patient was switched to daptomycin. Initially, source control was not planned for the patient; thus, additional antibiotics including ceftaroline 600 mg IV q8h, gentamicin 1 mg/kg IV q8h, and clindamycin 600 mg IV q8h were added to combat the persistent MRSA bacteremia. The patient received a laminectomy on Day 22, with the patient achieving the first set of negative blood cultures on Day 32. This combination may be considered for other patients who have failed traditional therapy for MRSA bacteremia.

Keywords: daptomycin; ceftaroline; gentamicin; clindamycin; methicillin-resistant *Staphylococcus aureus*; bacteremia; vertebral osteomyelitis

## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a substantial cause of community and healthcare associated infections, including MRSA bacteremia [1]. The first-line treatment for MRSA bacteremia is vancomycin or daptomycin for a minimum of 2 weeks starting from the first day of source control [1,2]. Treatment failure to vancomycin should be considered at or around day 7 of therapy based on the guidelines; however, some clinicians believe that treatment failure should be considered at 3-4 days due to poor outcomes and serious complications [1,3]. In this situation, high-dose daptomycin with another agent is recommended if susceptible [1,4]. These agents include rifampin, linezolid, trimethoprim/sulfamethoxazole, and  $\beta$ -lactam antibiotics [5]. Patient's clinical response, trough concentrations for vancomycin, susceptibilities, and source control are all factors to be contemplated for selection of therapy [5]. The following case report illustrates the management of persistent MRSA bacteremia with high vancomycin and daptomycin MICs, requiring the use of multiple antibiotics. Patient consent and Internal Review Board approval was obtained.

## CASE DESCRIPTION

A 63-year-old male with MRSA bacteremia secondary to vertebral osteomyelitis presented to the hospital with nausea, vomiting, back pain, and a temperature of 39°C. Blood cultures on admission showed MRSA with susceptibility to vancomycin (MIC=2 mcg/mL). Both trans-thoracic echocardiogram (TTE) and trans-esophageal echocardiogram (TEE) showed no vegetation. The impression from the MRI was discitis with enhancement at L2-3 and L3-4 which was more pronounced at L2-3. Initially the patient was not recommended for any neurosurgical or spinal intervention given the absence of any neurologic compromise and improvement in symptomatology with regards to pain. Upon admission the patient was started on piperacillin/tazobactam 3.375 grams IV every 8 hours infused over 4 hours and vancomycin (trough levels 11.9 to 18.6 mcg/mL, Days 5-7) (Figure 1). Cefazolin 2 gram IV every 6 hours was given from Day 2 to 6. On Day 8, antibiotics were changed to daptomycin 8 mg/kg IV daily due to worsening leukocytosis (WBC 15.15 K/mm<sup>3</sup>) and patient not clinically improving on vancomycin. Repeat blood cultures were collected on Days 3, 7, 10, 17, and 19, and they continued to reveal MRSA sensitive to vancomycin and daptomycin (MIC of 2 mcg/mL and  $\leq$

0.5–1 mcg/mL, respectively). Although agents like linezolid, clindamycin, and doxycycline were showing susceptible, they were not initially chosen because of their bacteriostatic nature and the deep-seated nature of the infection. On Day 20, the sensitivity of repeat blood culture changed, revealing MRSA that was non-susceptible to daptomycin (MIC=4) (WBC 7.69 K/mm<sup>3</sup>). The dose of daptomycin was then maximized to 10 mg/kg IV daily, and ceftaroline 600 mg IV every 8 hours was added and adjusted appropriately for renal function. Due to the persistent bacteremia and the worsening progression of the discitis revealed by MRI and CT images, a laminectomy of L1-L3 epidural abscess/discitis was performed on Day 22. On Day 24, the WBC increased to 11.04 K/mm<sup>3</sup> and the surgical cultures resulted as positive for MRSA. Gentamicin 1 mg/kg IV every 8 hours (SCr 0.5 mg/dL) was initiated and adjusted as necessary for renal function on Day 24. Although the patient was afebrile and the WBC ranged from 8-11 K/mm<sup>3</sup>, the patient continued to have persistent positive MRSA blood cultures on Day 26. Clindamycin 600 mg IV every 8 hours was added on Day 30. The first negative blood cultures were collected on Day 32, and the patient eventually continued to improve and was discharged from the hospital on Day 219.

## DISCUSSION

Our report presents a case for the management of persistent MRSA bacteremia and vertebral osteomyelitis where vancomycin was previously administered, and multiple antibiotics were required in addition to a laminectomy. Different antimicrobial monotherapy or combinations have been studied and presented, although the best approach in a patient with persistent MRSA bacteremia is yet to be determined [6]. There is a high likelihood of vancomycin therapy failure when the MRSA MIC = 2 mcg/mL, as the AUC/MIC target of  $\geq 400$  is only achieved when the MIC  $\leq 1$  mcg/mL with a goal trough is 15-20 mcg/mL. Daptomycin 10 mg/kg/day and ceftaroline were both administered to the patient (a ceftaroline e-test was not performed). Daptomycin works by inserting into the membrane of bacteria causing membrane damage and is active against most gram positive pathogenic organisms [7]. Daptomycin susceptibility is defined as a MIC  $\leq 1$  mcg/mL. The higher MICs which our patient presented with daptomycin ( $> 1$  mcg/mL) may be due to prior exposure to vancomycin despite not having been on daptomycin previously, and the fact that daptomycin frequently is resistant or becomes resistant quickly

*1*The University of North Texas Health Science Center System College of Pharmacy; Fort Worth, TX, USA; *2*Medical City Arlington, Arlington, TX, USA; *3*ID Partners DFW, Mansfield TX, USA

Correspondence: Ramanathan MR, The University of North Texas Health Science Center System College of Pharmacy, Fort Worth, TX, USA. Telephone 9728984793 e-mail: meenakshi.ramanathan@unthsc.edu

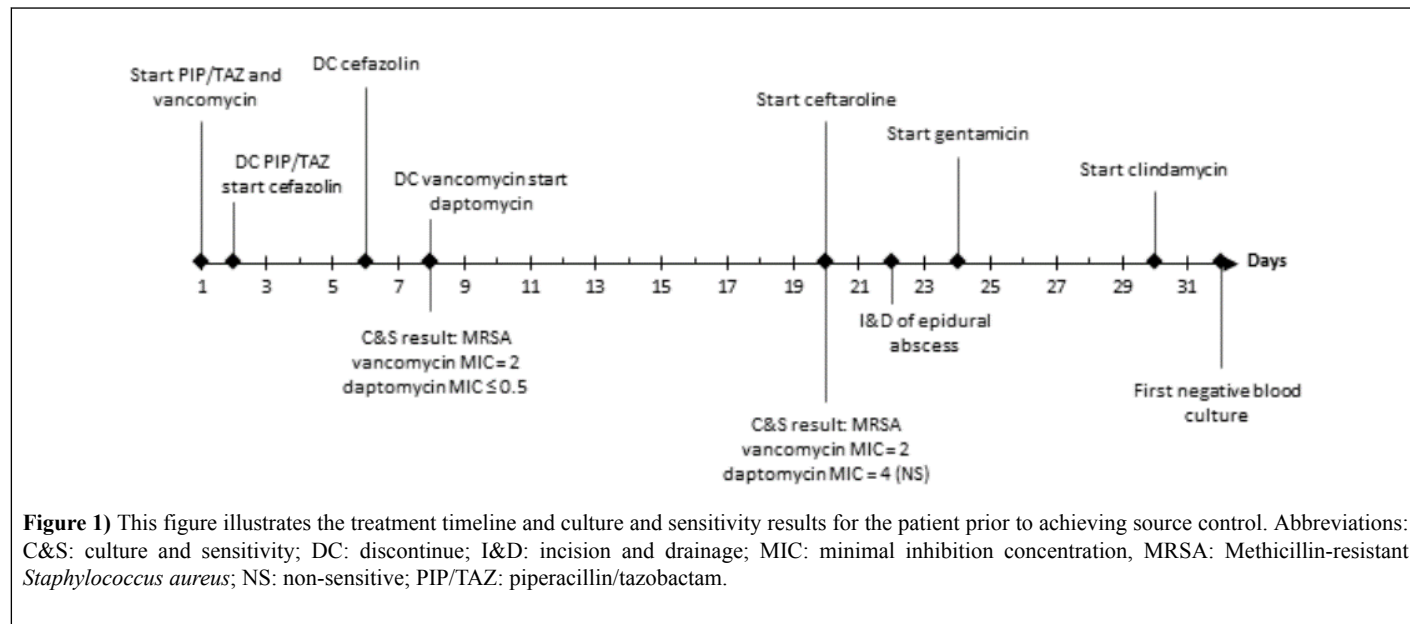
Received: June 22,2018, Accepted: September 25,2018, Published: September 28,2018



This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact [reprints@pulsus.com](mailto:reprints@pulsus.com)

when the MRSA strain has a MIC = 2 mcg/mL to vancomycin (1). Ceftaroline is similar to other  $\beta$ -lactams in exerting time-dependent killing, exposing the pathogen to the drug for an extended time period,

and it inhibiting cell wall synthesis by binding to penicillin-binding proteins [8].



In a pharmacokinetic/pharmacodynamic model, bactericidal activity was achieved when both ceftaroline and daptomycin were given concurrently in both daptomycin-susceptible and non-susceptible MRSA strains [9]. The synergistic mechanism by which this occurs is thought to be attributable to ceftaroline's ability to reduce cell wall thickness and increase the membrane binding of and enhance the activity of daptomycin (daptomycin-induced depolarization and killing by LL37) [9]. In one study, the median time for MRSA bacteremia clearance after the administration of daptomycin and ceftaroline was 2 days, ranging from 1 to 6 days [4]. In contrast to this study, our patient did not achieve the first set of negative blood cultures until 12 days after the combination of daptomycin and ceftaroline, along with 9 days of gentamicin and 3 days of clindamycin. Gentamicin was initiated for synergy when the patient's WBC increased and there was no improvement in clinical status. However, positive blood cultures continued to persist, and clindamycin was started. In the end, bacteremia clearance was documented on Day 32. Despite receiving appropriate antibiotics, the patient required several combinations of antibiotics to clear the MRSA bacteremia. A laminectomy of L1-L3 epidural abscess/discitis was performed on Day 22 because of persistent positive blood cultures and a worsening follow-up MRI. Removing the source of infection was critical in our patient. Poor source control and inadequate debridement can be reasons for MRSA bacteremia treatment failure [6]. Jongsma et al. reported a case of MRSA bacteremia and endocarditis with daptomycin failure that was most likely caused by a delay in surgical intervention of the abscess [10]. It is thought that clearance of the persistent MRSA bacteremia was achieved with adequate source control on Day 22 and the addition of clindamycin on Day 30. There are limited data to address how patients with persistent bacteremia should be treated optimally [6]. Resistance and failed therapies may create challenges in choosing the optimal drug regimen. The treatment of severe MRSA infections will continue to be shaped by the changes in MRSA epidemiology and clinical trials [11].

### CONCLUSION

Consideration of combination medications is necessary when the patient fails traditional regimens or if the patient has a prior history of failing traditional regimens. Our patient was placed on salvage treatment for the management of persistent MRSA bacteremia secondary to vertebral osteomyelitis due to the failure of traditional regimens. His salvage therapy consisted of high-dose daptomycin, ceftaroline, clindamycin, and gentamicin. This multi-drug regimen may be applicable to patients with persistent MRSA bacteremia when traditional therapy has failed. In

choosing an antimicrobial combination, the patient characteristics, condition, and risks such as adverse drug events versus benefits should be carefully considered. Further studies should be conducted to determine the safety and efficacy of salvage therapy.

### DISCLAIMER

This research was supported (in whole or in part) by HCA and/or an HCA affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA or any of its affiliated entities.

### REFERENCES

1. Liu C, Bayer A, Cosgrove SE. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52(3):18-55.
2. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. *JAMA* 2014;312(13):1330-41.
3. Kullar R, McKinnell JA, Sakoulas G. Avoiding the perfect storm: the biologic and clinical case for reevaluating the 7-day expectation for methicillin-resistant *Staphylococcus aureus* bacteremia before switching therapy. *Clin Infect Dis* 2014;59(10):1455-61.
4. Sakoulas G, Moise PA, Casapao AM, et al. Antimicrobial salvage therapy for persistent *Staphylococcal* bacteremia using daptomycin plus ceftaroline. *Clin Ther* 2014 Oct 1;36(10):1317-33.
5. Liu C. Management of MRSA Infections in Adult Patients 2011 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA). IDSA. 2011.
6. Kullar R, Sakoulas G, Deresinski S, et al. When sepsis persists: a review of MRSA bacteremia salvage therapy. *J Antimicrob Chemother* 2016;71(3):576-86.
7. Steenbergen JN, Mohr JF, Thorne GM. Effects of daptomycin in combination with other antimicrobial agents: a review of in vitro and animal model studies. *J Antimicrob Chemother* 2009;64(6):1130-8.
8. Houlbar M, Meng L, Deresinski S. Bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Infect Dis Clin North Am* 2016 Jun; 30(2):491-507.
9. Werth BJ, Sakoulas G, Rose WE et al. Ceftaroline increases membrane binding and enhances the activity of daptomycin against

## Management of persistent methicillin-resistant *Staphylococcus aureus* bacteremia with 32 days of positive blood cultures

- daptomycin-nonsusceptible                      vancomycin-intermediate  
*Staphylococcus aureus* in a pharmacokinetic/pharmacodynamic  
model. *Antimicrob Agents Chemother* 2013 Jan;57(1):66-73.
10. Jongsma K, Joson J, Heidari A. Ceftaroline in the treatment of  
concomitant methicillin-resistant and daptomycin-non-susceptible  
*Staphylococcus aureus* infective endocarditis and osteomyelitis: case  
report. *J Antimicrob Chemother* 2013 Jun;68(6):1444-5.
11. Rodvold KA, McConeghy KW. Methicillin-resistant *Staphylococcus  
aureus* therapy: past, present, and future. *Clin Infect Dis* 2014 Jan;58  
Suppl 1:S20-7.
- 
-